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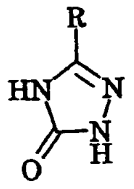
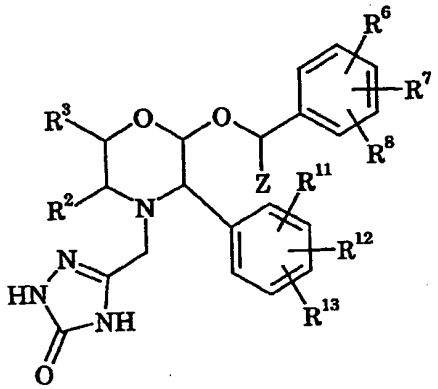
(54) Title: PROCESS FOR THE PREPARATION OF 1,2,4-TRIAZOLIN-5-ONE DERIVATIVES



(I)



(A)

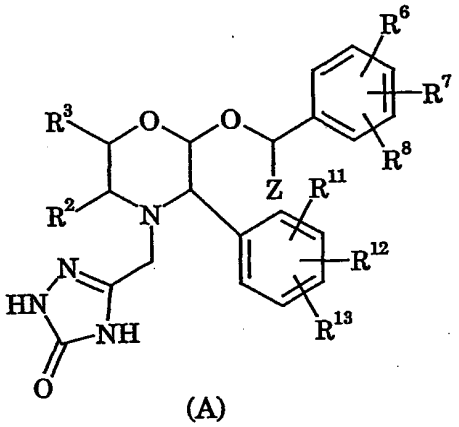
(57) Abstract: The present invention relates to a process for the preparation of a compound of formula (I) wherein R represents hydrogen, C_{1-10}alkyl, haloC_{1-10}alkyl or aryl; which are useful intermediates in the preparation of morpholine derivatives of formula (A). Compounds of formula (A) are useful as therapeutic agents.

WO 01/96315 A1

PROCESS FOR THE PREPARATION OF 1,2,4-TRIAZOLIN-5-ONE DERIVATIVES

The present invention relates to a process for the preparation of 1,2,4-triazolin-5-one derivatives which are useful as intermediates in the synthesis of therapeutic agents. In particular, the present invention relates to the preparation of the compound 3-chloromethyl-1,2,4-triazolin-5-one.

Compounds of formula (A), below, which are described in International patent specification No. WO 95/16679 (published 22nd June 1995), are potent and selective substance P (or neurokinin-1) receptor antagonists.



(A)

wherein

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) C_{2-6}alkenyl, and

(4) phenyl;

R^6, R^7 and R^8 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) fluoro,

(4) chloro,

(5) bromo,

(6) iodo, and

(7) $-CF_3$;

R^{11}, R^{12} and R^{13} are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) fluoro,

(4) chloro,

(5) bromo,

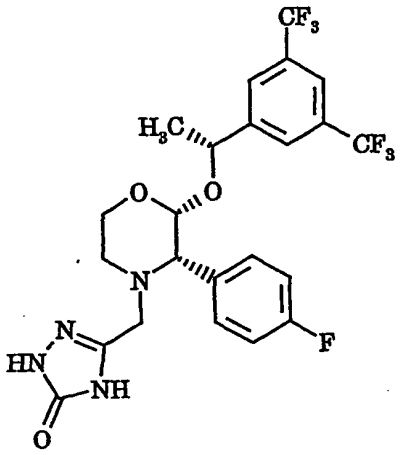
(6) iodo, and

(7) $-CF_3$; and

Z is C_{1-4}alkyl.

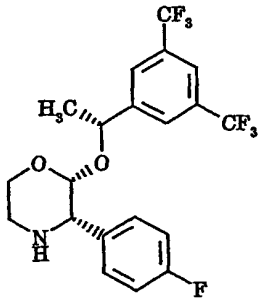
In particular, the compound 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine is a potent, long-lasting, nonpeptide substance P antagonist based upon its ability to displace [^{125}I]substance P from human NK_1 receptors (see Hale *et al.*, *J. Med. Chem.* (1998) 41, 4607). This compound is, therefore, a potential therapeutic candidate for a range of afflictions including chemotherapy-induced emesis, depression and anxiety.

International patent specification No. WO 95/16679 describes the preparation of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine (hereinafter referred to as Compound A), which has the structure:

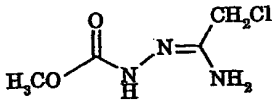


Compound A

by a two-step process starting from 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine. With reference to Examples 70 and 75 in WO 95/16679, Compound A is prepared as follows:

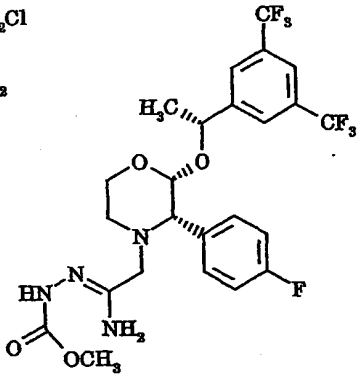


(from Ex. 74)

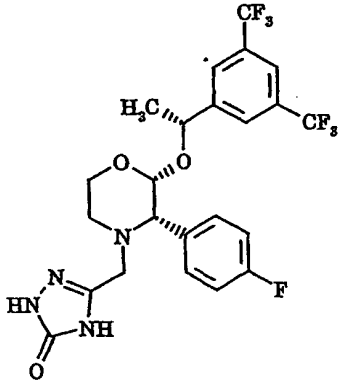


(from Ex.45)

DEA, CH_3CN

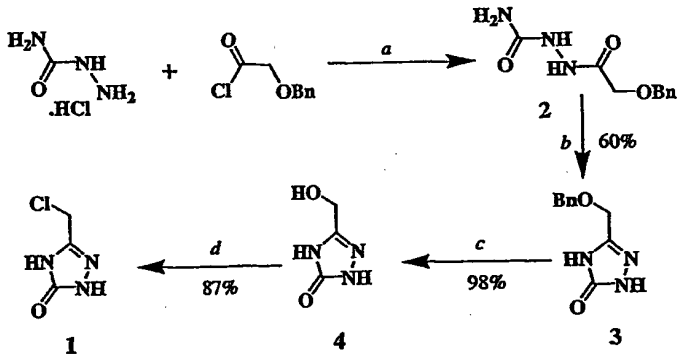


xylenes, reflux



Compound A

More recently, International Patent Publication No. WO 99/65900 (published 23 December 1999) described a convenient, efficient process which utilizes a one-step alkylation with 3-chloromethyl-1,2,4-triazolin-5-one. The synthesis of the chloromethyltriazolinone **1** is described in Examples 2 and 3 of WO 99/65900 which used the base-catalysed cyclisation of an acyl semicarbazide (**Scheme 1**). Hence, benzyloxyacetyl chloride was condensed with semicarbazide hydrochloride under modified Schotten-Baumann conditions to give crude adduct **2**. This was not purified but, instead, was heated in dilute NaOH to induce cyclisation thus giving triazolinone **3** in 60% yield from benzyloxyacetyl chloride. Hydrogenolytic removal of the benzyl protecting group, using ammonium formate as the hydrogen source, gave the water soluble alcohol **4** in excellent yield (98%). Treatment of this compound with thionyl chloride then afforded chloromethyltriazolinone **1** as a stable crystalline solid in 87% yield.



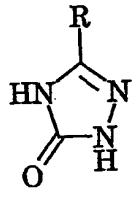
Scheme 1: (a) NaOH, THF/H_2O (5:1), 0 °C, 2 h; (b) NaOH (2M aq), reflux, 5 h; (c) Pd on C, HCO_2NH_4, MeOH/H_2O (10:1), 60 °C, 4 h; (d) $SOCl_2$, CH_3CN, 20 °C, 18 h.

While this synthesis of the chloromethyltriazole **1** allowed the study of the subsequent alkylation reaction to afford Compound A, the cost of the

starting acid chloride and the number of steps involved detracted from its viability for large scale synthesis.

There is therefore a need for a simple and efficient synthesis of 3-chloromethyl-1,2,4-triazolin-5-one and analogous compounds, that utilizes readily available starting materials.

Thus, in a first aspect of the present invention, there is provided a process for the preparation of a compound of formula (I)



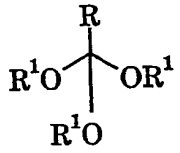
(I)

wherein

R represents hydrogen, C_{1-10}alkyl, haloC_{1-10}alkyl or aryl;

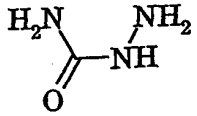
which comprises:

(i) reacting a triaryl- or trialkylorthoester of formula (II)



(II)

wherein each R^1 independently represents C_{1-10}alkyl, or aryl, with a semicarbazide of formula (III)



(III)

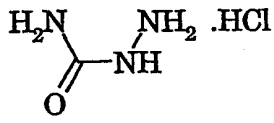
or a salt thereof, in an organic solvent; and

(ii) collecting the resultant compound of formula (I).

In the compounds of formulae (I) and (II), preferably R is hydrogen or, more particularly, a halomethyl group, especially chloromethyl.

In the compounds of formula (II), preferably each R^1 is the same. In particular, R^1 is preferably a methyl group.

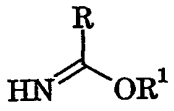
A salt of the compound of formula (III) is preferably used such as a halide, especially the chloride. In other words, the compound of formula (III) is semicarbazide.HCl – i.e.



Suitable organic solvents of use in the above reaction include alcohols. Most preferably, the above reaction is effected in methanol.

Conveniently, the above reaction is effected at room temperature.

According to an alternative aspect of the present invention, the compound of formula (I) may be prepared by the reaction of a compound of formula (IV)

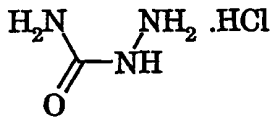


(IV)

or a salt thereof, wherein R and R^1 are as previously defined, with a compound of formula (III) in the presence of an alcoholic solvent.

This reaction proceeds via the *in situ* formation of an orthoester of formula (II). Thus, in the compound of formula (IV), R^1 is preferably a methyl group, and the solvent is preferably methanol.

A salt of the compounds of formula (IV) is preferably used such as a halide, especially the chloride. In other words, the compound of formula (III) is semicarbazide.HCl – i.e.



As used herein, the term "C_{1-10}alkyl" as a group or part of a group, means a straight or branched alkyl group containing from 1 to 10 atoms. Particularly preferred are C_{1-6}alkyl groups including methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Especially preferred is methyl.

As used herein, the term "haloC_{1-10}alkyl" means a straight or branched alkyl group containing from 1 to 10 carbon atoms wherein said alkyl group is substituted by one or more halogen atoms. Suitable halogen atoms include chlorine, bromine or iodine, most especially chlorine. Preferably said alkyl group is substituted by one halogen atom.

As used herein, the term "aryl" means an aromatic radical such as phenyl, biphenyl or naphthyl, wherein said phenyl, biphenyl or naphthyl group may be optionally substituted by one, two or three groups independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, NO_2, cyano, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxyC_{1-4}alkyl or $-O(CH_2)_mO-$, where R^a is hydrogen, C_{1-4}alkyl or fluoroC_{1-4}alkyl. Preferably said phenyl, biphenyl or naphthyl group is optionally substituted by one or two substituents, especially none or one. Particularly preferred substituents include fluorine, chlorine, bromine, methyl, methoxy, trifluoromethyl and trifluoromethoxy. Most preferably, aryl is a phenyl group.

According to a further aspect of the present invention, there is provided a method for the synthesis of the compounds described in

International Patent Publication No. WO 95/16679. In particular, there is provided a method for the synthesis of compounds of formula (A) as described herein. Said method comprises the preparation of a compound of formula (I) according to the method described and claimed herein, followed by one or more synthetic steps to complete the synthesis of the desired compound. Suitable methods for completing the synthesis are described, in particular, in International Patent Publication No. WO 99/65900.

In particular, there is provided the use of a compound of formula (I) when prepared according to the method described and claimed herein in the preparation of the compound 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine; and pharmaceutically acceptable salts thereof.

According to a yet further aspect of the present invention, there is provided the compound 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)-ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine, or a pharmaceutically acceptable salt thereof, prepared by the reaction of a compound of formula (I) with 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine, characterised in that said compound of formula (I) is prepared according to the method described and claimed herein. Suitable methods for completing the synthesis are described, in particular, in International Patent Publication No. WO 99/65900.

The following non-limiting examples illustrate processes according to the present invention:

EXAMPLE 1

3-Chloromethyl-1,2,4-triazolin-5-one

A mixture of semicarbzide hydrochloride (5.69 Kg, 51.0 mol), 2-chloro-1,1,1-trimethoxy ethane (94.0 mol) and methanol (54 L) was

stirred at room temperature for 4 days. The solvent was then removed under reduced pressure and toluene (25 L) was added. The resulting slurry was cooled to 0°C and filtered to afford 3-chloromethyl-1,2,4-triazolin-5-one (6.69 Kg, 98%) as a white solid (mp 197-199°C); ^{1}H NMR (d_6 DMSO) δ = 4.43 (2H, s, $C\underline{H}_2$), 11.48 (1H, s, N$\underline{H}$) and 11.64 (1H, s N$\underline{H}$); ^{13}C NMR (d_6 DMSO) δ = 36.9 (Cl$\underline{C}H_2$), 144.6 ($CH_2\underline{C}$=N) and 156.9 (NH$\underline{C}$ONH). The difficulty in following the reaction of such water soluble compounds has been overcome using the following HPLC conditions:

Column:	Waters Symmetry Shield RP8, 25cm x 4.6mm i.d.
Column Temperature:	45°C
Flow Rate	1.0 mL/min
Solvent Programme	100% A for 15 min then 50% A for 5 min then 100%A for 5 min.
Solvent A:	1 mL of 99.999% phosphoric acid (85 w/w%) is dissolved in 1 litre of water.
Solvent B:	Far U.V. HPLC grade acetonitrile is used neat in the solvent reservoir.
Retention time:	7.07 min

EXAMPLE 2

1,2,4-Triazolin-5-one

A mixture of semicarbazide hydrochloride (10.0 g, 89.6 mmol), trimethyl orthoformate (28.5 g, 269 mmol) and methanol (100 mL) was stirred at room temperature for 2 hours. The reaction was concentrated under reduced pressure and then toluene (100 mL) was added and, after cooling to 0°C, filtration gave the title compound (7.26 g, 100%) as a white solid; ^{1}H NMR (d_6 DMSO) δ = 7.66 (1H, s, C$\underline{H}$), 11.24 (1H, s, N$\underline{H}$) and 11.35 (1H, s, N$\underline{H}$); ^{13}C NMR (d_6 DMSO) δ = 137.0 ($CH_2\underline{C}$=N) and 156.6 (NH$\underline{C}$ONH).

REFERENCE EXAMPLE A

Preparation of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine

A solution of 3-chloromethyl-1,2,4-triazolin-5-one (3.18 g) in DMF (30 ml) was added over 1 hour to a slurry of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine (R)-camphor sulfonic acid salt (15 g) and potassium carbonate (7.71 g) in DMF (100 ml) at 22°C. The reaction mixture was aged at 22°C for 20 minutes, then water (400 ml) was added over 30 minutes. The crystallising mixture was cooled in an ice bath, aged for 30 minutes and the product collected by filtration. The solid title compound was washed with water (400 ml), air dried and dried *in vacuo* at 45-50°C. Yield = 11.4 g; 98.1% HPLC w/w assay; 93.2% assay yield; (97.1A% HPLC profile).

REFERENCE EXAMPLE B

Alternative Preparation of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)-ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine

(1) B1:- Alternative Method using N,N-diisopropylethylamine/DMF

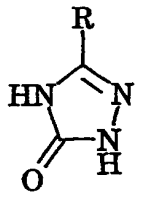
A solution of 3-chloromethyl-1,2,4-triazolin-5-one (2.56 g) in DMF (20 ml) was added over 1 hour to a slurry of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine *para*-toluenesulfonic acid salt (12 g) and N,N-diisopropylethylamine (5.15 g) in DMF (40 ml) at 21°C. The reaction was aged at 21-23°C for 30 minutes, then water (120 ml) was added over 20 minutes. The crystallising mixture was cooled in an ice bath, aged for 30 minutes and the product collected by filtration. The solid title compound was washed with water (96 ml), air dried and dried *in vacuo* at 50°C. Yield = 9.65 g; 99.7% isolated yield.

(2) B2:- Alternative Method using potassium carbonate/DMF

A solution of 3-chloromethyl-1,2,4-triazolin-5-one (1.40 g) in DMF (13.5 ml) was added over 1 hour to a slurry of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine *para*-toluenesulfonic acid salt (6.77 g) and potassium carbonate (1.55 g) in DMF (27 ml) at 19°C. The reaction was aged at 19-21°C for 30 minutes, then water (81 ml) was added over 20 minutes. The crystallising mixture was cooled in an ice bath, aged for 30 minutes and the product collected by filtration. The solid title compound was washed with water (54 ml), air dried and dried *in vacuo* at 50°C. Yield = 5.37 g; 98.0% HPLC w/w assay; 96.4% assay yield.

CLAIMS

1. A process for the preparation of a compound of formula (I)



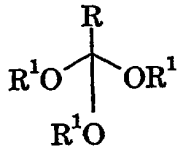
(I)

wherein

R represents hydrogen, C_{1-10}alkyl, haloC_{1-10}alkyl or aryl;

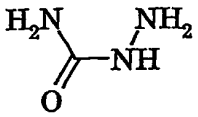
which comprises:

(i) reacting a triaryl- or trialkylorthoester of formula (II)



(II)

wherein each R^1 independently represents C_{1-10}alkyl, or aryl, with a semicarbazide of formula (III)



(III)

or a salt thereof, in an organic solvent; and

(ii) collecting the resultant compound of formula (I).

2. A process according to Claim 1 wherein, in the compounds of formulae (I) and (II), R is hydrogen or a halomethyl group.

3. A process according to Claim 2 wherein, in the compounds of formulae (I) and (II), R is a chloromethyl group.

4. A process according to Claim 1 wherein, in the compounds of formula (II), each R^1 is the same.

5. A process according to Claim 4 wherein each R^1 is a methyl group.

6. A process according to Claim 1 wherein said compound of formula (III) is in the form of a halide salt.

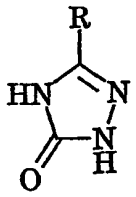
7. A process according to Claim 6 wherein said halide salt is the hydrochloride salt.

8. A process according to Claim 1 wherein said organic solvent is an alcohol.

9. A process according to Claim 9 wherein said alcohol is methanol.

10. A process according to Claim 1 wherein said process is effected at room temperature.

11. A process for the preparation of a compound of formula (I)



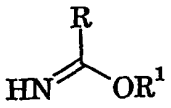
(I)

wherein

R represents hydrogen, C_{1-10}alkyl, haloC_{1-10}alkyl or aryl;

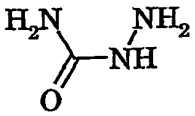
which comprises:

(i) the reaction of a compound of formula (IV)



(IV)

or a salt thereof, wherein R is as previously defined and each R^1 independently represents C_{1-10}alkyl, or aryl, with a compound of formula (III)



(III)

or a salt thereof, in an organic solvent; and

(ii) collecting the resultant compound of formula (I).

12. A process according to Claim 11 wherein, in the compound of formula (IV), R is a chloromethyl group.

13. A process according to Claim 11 wherein, in the compound of formula (IV), R^1 is a methyl group.

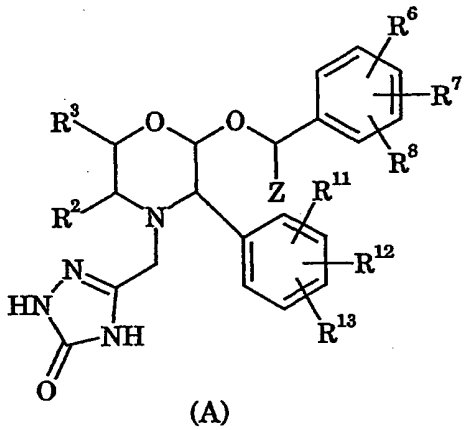
14. A process according to Claim 11 wherein said compound of formula (III) is in the form of a halide salt.

15. A process according to Claim 14 wherein said halide salt is the hydrochloride salt.

16. A process according to Claim 11 wherein said organic solvent is an alcohol.

17. A process according to Claim 16 wherein said alcohol is methanol.

18. A process for the preparation of a compound of formula (A)



(A)

wherein

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) C_{2-6}alkenyl, and

(4) phenyl;

R^6, R^7 and R^8 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) fluoro,

(4) chloro,

(5) bromo,

(6) iodo, and

(7) $-CF_3$;

R^{11}, R^{12} and R^{13} are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) fluoro,

(4) chloro,

(5) bromo,

(6) iodo, and

(7) $-CF_3$; and

Z is C_{1-4}alkyl;

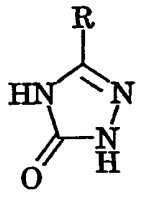
or a pharmaceutically acceptable salt thereof,

wherein said process comprises the preparation of a compound of formula (I) according to any one of Claims 1 to 17, followed by one or more synthetic steps to complete the synthesis of the desired compound of formula (A).

19. A process according to Claim 18 wherein the compound of formula (A) is 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine; or a pharmaceutically acceptable salt thereof.

20. A process according to Claim 18 or Claim 19 wherein the compound of formula (I) is 3-chloromethyl-1,2,4-triazolin-5-one.

21. The compound 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)-ethoxy)-3-(*S*)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine; or a pharmaceutically acceptable salt thereof, prepared by the reaction of 2-(*R*)-(1-(*R*)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(*S*)-(4-fluorophenyl)morpholine with a compound of formula (I)



(I)

wherein

R represents hydrogen, C_{1-10}alkyl, haloC_{1-10}alkyl or aryl;

characterised in that said compound of formula (I) is prepared according to any one of Claims 1 to 17.

22. The compound according to Claim 21 wherein said compound of formula (I) is 3-chloromethyl-1,2,4-triazolin-5-one.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[redacted]1/02617

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D249/12 C07D413/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	K. KAMATA ET AL: "Synthesis of optically active 2-chloromethyl-2-oxazolines by the ortho-ester condensation method using triethylorthochloroacetate" HETEROCYCLES., vol. 51, no. 2, 1 February 1999 (1999-02-01), pages 373-378, XP002176381 ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM., NL ISSN: 0385-5414 the whole document	1-10
Y	WO 99 18089 A (LONZA AG ;VEITH ULRICH (CH)) 15 April 1999 (1999-04-15) claims	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 August 2001	14/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Chouly, J

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INTERNATION. SEARCH REPORT

Int ... plication No
PCT/ ...1/02617

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 65900 A (MERCK SHARP & DOHME ;HANDS DAVID (GB); COTTRELL IAN FRANK (GB); WI) 23 December 1999 (1999-12-23) cited in the application claims	1-22
P,X	C.J. COWDEN: "A new synthesis of 1,2,4-triazolin-5-ones: application to the convergent synthesis of an NK1 antagonist" TETRAHEDRON LETTERS, no. 41, 28 October 2000 (2000-10-28), pages 8661-8664, XP004236142 OXFORD GB the whole document	1-22

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Inte [redacted]plication No
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		EP 1023272 A	02-08-2000
		US 6248900 B	19-06-2001
WO 9965900 A	23-12-1999	AU 4281399 A	05-01-2000
		BR 9911250 A	13-03-2001
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		EP 1087966 A	04-04-2001